REMARKS

With this response, claims 21-43 are pending. Claims 1-20 have been cancelled without prejudice or disclaimer, and new claims 21-43 have been added by way of the present amendment. Support for the amendments and new claims can be found throughout the specification and the claims as originally filed. Additional support for such amendments and new claims will be apparent to one of skill in the art.

I. Information Disclosure Statement

Again, it is noted that the Examiner-initialed copy of the PTO-1449 form submitted by Applicant on January 3, 2002 and returned by the Examiner with the Office Action mailed July 16, 2002, includes both Examiner initialing indicating consideration of certain cited references and lining thorough indicating that the cited references were not considered. Clarification is requested. If additional copies of references are required, please advise.

II. Objection to the Claims

Claim 8 has been objected to under 35 C.F.R. § 1.75(c) as being in the improper form of multiple dependent claim depending from another multiple dependent claim, i.e., claim 7 herein. This objection is respectfully traversed. "A multiple dependent claim shall not serve as a basis for any other multiple dependent claim." 35 U.S.C. § 112, Fifth Paragraph. However, claim 8 is not a multiple dependent claim and properly depends from claim 7. Nonetheless, in order to facilitate prosecution, claims 7 and 8 have been cancelled without prejudice. Therefore, this objection is moot and withdrawal of this objection is respectfully requested.

III. Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-20 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling one of skill in the art to make and/or use the invention. This rejection is respectfully traversed for at least the reasons that follow.

The Examiner acknowledges that the specification is enabled for conjugating PEG polymer to exendin-4 peptide, and for use of the exendin peptide (non-conjugated) for decreasing glucagon secretion in a patient having glucagonoma or Type II diabetes. *Office Action, Paper*

No. 22, at page 2. However, the Examiner asserts that the specification "does not reasonably provide enablement for using the [] polymer modified exendin conjugates to decrease glucagon level in the patient thereof." *Id.* (emphasis in original).

Applicants respectfully traverse this rejection. Applicants have provided considerable direction and guidance, and have presented working examples such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation. For instance, based on the guidance provided in the specification regarding the therapeutic activity of exendins, the mechanism of *in vivo* clearance of exendins, and the coupling of polymer-moieties to exendins and exendin analogs, it is well within the level of ordinary skill in the art to design therapeutically active polymer-modified exendins and exendin analogs without the need for undue experimentation.

Further, Applicants respectfully traverse the Examiner's allegation that the claimed invention "involves highly variant PEG-modified exendin conjugates" and that the outcome of administering such conjugates is "unpredictable in the absence of factual indicia to the contrary." *Office Action, Paper No. 22*, at page 6. The Examiner appears to rely on the concept that "different diseases require different therapeutic procedures and protocols as well as doses and forms of pharmaceutics." *Id.* Even assuming *arguendo* that such a concept is accurate, determination of such procedures and protocols is well within the level of skill in the art once a candidate glucagonostatic agent is identified. Further, it is submitted that the specification discloses sufficient guidance to render the results predictable within the context of the exendin compounds of the invention. In fact, by providing guidance as to the selection of exendin compounds, the design of polymer-modifications to such exendin compounds, and the demonstration of glucagonostatic activity consistent with such guidance, Applicants have demonstrated that the present invention yields a predicted result.

Applicants also respectfully traverse the Examiner's allegation that:

> One of skill in the art would not know . . . whether the exendin analog encompasses any structural or/and functional derivative, e.g., GLP-1 which has the same effect as exendin-4 on decreasing glucagon level.

Office Action, Paper No. 22, at page 4.

By way of background, it is noted that analogs of a molecule are structurally related to the molecule, while agonists are functionally related to the molecule. This distinction is made clear in the disclosure that "exendin agonists include exendin peptide analogs in which one or more naturally occurring amino acids are eliminated or replaced with another amino acid(s). Preferred exendin agonist are agonist analogs of exendin-4." *Specification*, page 19. Additional direction and guidance are provided in many commonly owned applications disclosing exendin analogs, all of which are incorporated in their entireties into the present application. *Id.* The exendin analogs of the present application encompasses structurally related exendin analogs that are also functionally related to exendin with regard to the therapeutic lowering of glucagon levels, *i.e.*, exendin analogs which exhibit therapeutic glucagon lowering activity, but not any "functional derivative" of exendin. Specifically, GLP-1 is not an exendin analog within the meaning of the present application.

Nonetheless, in order to facilitate prosecution, the claims have been amended without prejudice to remove reference to polymer-modified exendin peptides. It is submitted that the specification enables one of skill in the art to practice the invention commensurate in scope with the presently pending claims. Accordingly, for at least these reasons, it is submitted that the claims are sufficiently enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-20 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed for at least the reasons which follow.

The Examiner acknowledges that "Applicant is in possession of "the unmodified exendin-4 for decreasing glucagon levels in a patient suffering from disease, e.g., glucagonoma, and PEG-modification of exendin-4." *Office Action, Paper No. 22* at page 10. However, in support of this rejection, the Examiner alleges that:

> Applicant is not in possession of any polymer-modified exendin molecules, any exendin analogs and any polymer-modified exendin analog compounds, and not in [] possession of a method of lowering plasma glucagon in a subject comprising administering the polymer-modified exendin or polymer-modified exendin analog to said subject to treat glucagonoma, glucagonoma associated necrolytic migratory erythema, or Type II diabetes.

Office Action, Paper No. 22, at page 10 (emphasis in original). Applicants respectfully disagree. Applicants also traverse the Examiner's assertion that exendin 1, 2, 3, and 4 are related to the glucagon family. Exendin-4 is the product of a gene in the lizard that is distinct from the proglucagon gene that produces lizard glucagon and lizard glucagon-like protein 1 (GLP-1) (homologs to the mammalian counterparts). As such, it is submitted that the exendin peptide family is distinct from the glucagon-like family. The Examiner's reference is directed to copending, co-owned U.S. Patent Application No. 09/019,172 entitled "Polynucleotides Encoding Proexendin, and Methods and Uses Thereof," which describes the identification of the proglucagon gene as distinct from the GLP-1 gene in further detail.

Nonetheless, in order to facilitate prosecution, the claims have been amended without prejudice to remove reference to polymer-modified exendin peptides. It is submitted that the present specification, including the incorporated commonly owned applications, clearly demonstrates that Applicants are in possession of the claimed genus of exendin analogs. More particularly, as described above and in previous responses, Applicants have provided sufficient guidance and working examples as to structural and functional characterization of the claimed exendin peptides, *e.g.*, through extensive disclosure of exendin analog sequences and assays for verifying activity in glucagon suppression. It is submitted, therefore, that the present claims meet the written description requirement, and withdrawal of this rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 112, Second Paragraph, Definiteness

Claims 1-20 stand rejected under 35 U.S.C. § 112 as allegedly indefinite in that the recitations "therapeutic lowering," "exendin analog," "polymer-modified exendin," and "polymer-modified exendin analog" lack antecedent bases in the specification. This rejection is respectfully traversed. It is submitted that one of skill in the art would be apprised of the scope of the present claims.

More particularly, the Examiner asserts that the term "therapeutic lowering of plasma glucagon" in claim 1 is indefinite because "the specification does not define the phrase 'therapeutic lowering[' and] the recitation is unclear as to whether or not therapeutic lowering refers to in vivo lowering process or a drug treatment associated process." *Id.* at page 13. It is submitted that one of skill in the art will readily appreciate that "therapeutic lowering of plasma glucagon" refers to administering to a subject a therapeutically effective amount of drug to achieve the effect of lowering the *in vivo* plasma glucagon level. Additionally, the recitation "therapeutic lowering of plasma glucagon" finds antecedent basis in the present specification. *See* page 11, lines 18-19, and page 18, lines 4-11 of the present application; *see also* claim 1. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner also asserts that the term "exendin analog" is unclear because the specification allegedly fails to provide a definition of the term, and because the recitation is allegedly unclear regarding whether or not the recitation encompasses exendin agonists, antagonists and/or chemically modified exendins. Applicants respectfully traverse. As discussed above, analogs of a molecule are structurally related to the molecule, while agonists are functionally related to the molecule. This distinction is made clear in the disclosure that "exendin agonists include exendin peptide analogs in which one or more naturally occurring amino acids are eliminated or replaced with another amino acid(s). Preferred exendin agonist are agonist analogs of exendin-4." The specification, including incorporated documents, therefore makes clear that analogs may be a subset of agonists within the context of the invention. Further, when read in the context of the claim as a whole, it is clear that the claimed exendin analogs are administered in therapeutically glucagon lowering amounts. As such, one of skill in the art would clearly comprehend that the claimed exendin analogs exhibit exendin agonist activity. It is thus submitted that the claim term "exendin analog" is clear and definite, and withdrawal of this rejection is respectfully requested.

Further, the Examiner has asserted that the claim terms relating to "polymer-modified exendins" are indefinite. Although Applicants respectfully traverse this rejection, the claims have been amended without prejudice to omit the recitations polymer-modified exendin peptides. Withdrawal of this rejection is therefore respectfully requested.

Claims 7 and 14 also stand rejected as allegedly indefinite. These claims have been cancelled without prejudice or disclaimer. As such, withdrawal of these rejections are respectfully requested.

V. Rejection under 35 U.S.C. § 102

A. U.S. Patent No. 5,424,286 to Eng et al.

Claims 1-5, 10-13, 15, 17, and 20 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,424,286 to Eng et al. ("Eng"). This rejection is respectfully traversed for at least the reasons which follow. Initially, it is submitted that Eng fails to teach, disclose or suggest the ability of exendins to lower glucagon levels or the benefits of the therapeutic lowering of glucagon levels, much less the identification of a subject in need of lowering of glucagon levels.

Nonetheless, in support of this rejection, the Examiner alleges that

> Eng teaches that an insulinotropic peptide, e.g., glucagon-like insulinotropic peptide (GLIP) significantly lowers the plasma concentrations of insulin and glucagon . . ., and explicitly teaches that, exendin-4 is an insulinotropic agent . . . Thus, lowering plasma glucagon in a subject [by exendin-4] is inherent in the [Eng] patent.

Office Action, Paper No. 22, at pages 16 and 18.

The Examiner appears to be correlating insulinotropism with glucagon suppression to conclude that all insulinotropic agents necessarily suppress glucagon levels. Applicants submit that such a conclusion finds no support in the cited art.

More particularly, glucagon suppression (*i.e.*, being glucagonostatic) and stimulation of insulin secretion (*i.e.*, insulinotropism or being insulinotropic) are distinct functions. In this regard, Applicants note that insulin is secreted by pancreatic β-cells, while glucagon is secreted by pancreatic α-cells. As such, one of skill in the art would not expect glucagon suppression to correlate to insulin secretion. For example, the human hormone amylin is known to suppress glucagon, yet does not stimulate insulin secretion. Moreover, the insulinotropic effects of GLP-1 result, at least in part, from direct action on GLP-1 receptors of pancreatic β-cells. However, pancreatic α-cells, where glucagon is secreted, do not include GLP-1 receptors. One of skill in

the art would therefore not necessarily expect the insulinotropic effects of either GLP-1 or exendin to correlate with their effects on glucagon suppression. As such, it is submitted that one of skill in the art would not assume that glucagon suppression and insulinotropism are inherently linked.

The Examiner further asserts that "[t]he Eng's patent also teaches treatment of patient suffering from non-insulin dependent diabetes mellitus (NIDDM) who has increase in plasma concentration of glucagon by administering to the subject (patient) effective insulinotropic amount of exendin-4 (SEQ ID NO: 2)" *Id.* at page 16. The Examiner appears to be concluding that the treatment of a NIDDM patient inherently teaches a method of lowering plasma glucagon. Applicants respectfully traverse. The claims are directed to a method of lowering plasma glucagon in a patient in need thereof. The Federal Circuit has directly addressed this issue of claim interpretation, and held that "the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. [. . .] The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed." *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003) (*citations omitted*). The present claims therefore require that the method be performed for the stated purpose of lowering plasma glucagon. As such, Eng's suggestion of treating NIDDM does not teach a method of lowering plasma glucagon in a patient in need thereof.

Additionally, contrary to the Examiner's assertion that SEQ ID NO: 2 of Eng reads on SEQ ID NO: 47 and SEQ ID NO: 48 of the present claims, it is noted that SEQ ID NOs: 47 and 48 of the present application specifically exclude the sequence of exendin-3 and exendin-4 from their scope. As such, Eng's SEQ ID NO: 2 (exendin-4) does not in fact read on SEQ ID NOs: 47 and 48 of the present application. For this additional reason, Eng does not anticipate presently pending dependent claims 28-31 and 39-42.

In sum, whatever else Eng does teach, it does not disclose the presently claimed invention. For at least these reasons, it is respectfully submitted that Eng does not anticipate the present claims. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

B. Marketletter Published 24 August 1998

Claims 1-3 and 10-13 also stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Marketletter published 24 August 1998 ("Marketletter"). This rejection is respectfully traversed for at least the reasons which follow.

Even assuming *arguendo* that Marketletter is available as prior art, it is submitted that Marketletter does not anticipate the present claims. Contrary to the Examiner's assertions, Marketletter simply does not disclose the ability of exendin-4 to inhibit glucagon secretion. As discussed above, the insulinotropic activity of exendin-4 does not automatically lead one of skill in the art to the conclusion that exendin-4 suppresses glucagon. The passing reference in Marketletter concerning inhibition of glucagon secretion refers to the activity of glucagon-like peptide-1. Although there is suggested comparison of exendin-4 to GLP-1 with regard to insulinotropic activity, there is no indication in the prior art of record that exendin-4 would act in a manner similar to that of GLP-1 with regard to glucagonostatic activity. Marketletter provides no enabling disclosure that exendin-4 would be expected to act exactly like GLP-1 in all instances, much less in the specific instance of glucagon suppression.

In sum, it is respectfully submitted that Marketletter does not anticipate the present claims, as it does not disclose, teach or suggest the ability of exendin-4 to inhibit glucagon secretion. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

VI. Rejection under 35 U.S.C. § 103

Claims 1-20 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Eng, taken in combination with Marketletter, U.S. Patent No. 6,051,557 to Drucker ("Drucker"), WO 98/30231 to Young *et al.* ("Young"), and U.S. Patent No. 4,179,397 to Frank ("Frank"). This rejection is respectfully traversed for at least the reasons that follow.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on Applicants' disclosure. *See* M.P.E.P. §§ 2143.01 and 2143.03.

As discussed above, it is submitted that Eng and Marketletter do not disclose, teach or suggest the ability of exendin peptides to inhibit glucagon secretion. Drucker, Young, and Frank do nothing to provide a teaching or suggestion as to the benefits of the therapeutic lowering of glucagon levels or the glucagonostatic activity of exendins peptides. It is impermissible hindsight to find it obvious for one skilled in the art to combine the various prior art references to reach the invention in the present application.

Nonetheless, the claims have been amended without prejudice to remove reference to polymer-modified exendin peptides. As such, Applicants respectfully submit that the cited references do not render the present claims obvious, since significant limitations of the claims are neither taught nor suggested by the cited references. Withdrawal of this rejection is therefore respectfully requested.

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objection and rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-6111 should any additional information be necessary for allowance.

Respectfully submitted,

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